

**MELATONIN, THE HORMONE OF DARKNESS:
A RAY OF HOPE FOR MANY DISEASES**

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Summary:

Melatonin plays a major role in synchronizing internal biologic events to the external environment. The hormone is mainly secreted by the pineal gland. The secretion is regulated by the suprachiasmatic nuclei of the hypothalamus with the light/dark cycle being the main synchronizer. MT₁ and MT₂ are the two main types of receptors. Melatonin promotes sleep, regulates reproduction, circadian rhythms, immunoresponsiveness and inhibits aging and cancer growth.

Melatonin has been shown to be useful in treatment of jet lag and delayed sleep phase syndrome. Treatment of insomnia in the elderly, tapering of hypnotics, treatment of cancer, amelioration of the toxicity of cancer chemotherapy and entraining circadian rhythms in the blind are other indications. Melatonin has been used for preoperative sedation and in neurodegenerative disorders and stroke. The drug has shown promise as a radioprotective agent.

Drug-drug interactions can be a problem. Agomelatine and Ramelteon are melatonin receptor agonists and are showing clinical promise. Melatonin and its congeners will play an important role in therapeutics.

Key words: Agonists, Melatonin, Therapeutic uses

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Melatonin lightens the frog skin by contracting the pigment containing melanophores. Lerner, Case and Takahashi discovered the skin-lightening effect way back in 1958 [1].

Life on earth follows 24-hour rhythmicity due to the rotation of the earth around its axis. Many body processes such as sleep, core body temperature, serum cortisol and others follow a regular circadian rhythm. Melatonin is the main element in synchronization of internal biologic events to the environment. Melatonin is secreted exclusively at night in both nocturnal and diurnal species [2]. Melatonin may thus be considered as a 'hormone of darkness'.

Secretion of melatonin:

Around three centuries ago, Rene Descartes, a French philosopher described the pineal gland. However, melatonin, the principal substance secreted by the gland was isolated only in the late 1950s. Melatonin is the main hormone secreted by the pineal gland. Other sources are the retina, gut, skin, platelets and bone marrow [3,4]. The Harderian gland, the membranous cochlea and gastrointestinal tract (GIT) also secrete melatonin. The GIT contains several hundred times more melatonin than the pineal gland [5]. However, extra pineal sites contribute poorly to circulating melatonin.

Biosynthesis:

Tryptophan is taken from the circulation and converted to serotonin. The sequential activity of two enzymes, serotonin-N-acetyl transferase (NAT), the rate limiting enzyme and hydroxyindole-O-methyl transferase (HIOMT) converts serotonin to melatonin [6].

Structure and its significance:

Melatonin is chemically N-acetyl-5-methoxytryptamine. The two functional groups are involved in specificity of binding and amphiphilicity of the molecule, allowing it to enter any cell, body compartment and fluid [7]. The structure allows melatonin to scavenge oxygen-derived reactants including hydroxyl (OH) radical, hydrogen peroxide (H₂O₂), singlet oxygen (1O₂) and hypochlorous acid (HOCl) [8]. Melatonin also reacts with nitric oxide (NO), peroxy nitrite anion (ONOO⁻) and peroxy nitrous acid (ONOOH) to detoxify them.

Regulation of melatonin secretion:

The secretion of melatonin is regulated by the suprachiasmatic nuclei (SCN) of the hypothalamus [9]. The light/dark cycle is the main synchronizer or zeitgeber of the system regulating melatonin secretion. The photic information is transmitted to the central pacemaker (SCN) via the retino-hypothalamic fibers. Output from the tract inhibits melatonin synthesis and secretion. Artificial light (of sufficient intensity and duration) when administered at night can suppress melatonin production [10].

The neural pathway from the SCN to the pineal gland synapses in the superior cervical ganglia of the sympathetic chain. At night, the SCN stimulates the ganglion releasing norepinephrine (NE). NE acts on the pineal gland releasing melatonin [9].

Other neurotransmitters like neuropeptide Y, vasoactive intestinal peptide (VIP) and substance P modulate the effect of NE.

Melatonin receptors:

The receptors were originally classified as ML₁ (high affinity) and ML₂ (low affinity) receptors. Molecular cloning revealed that there are at least three subtypes of ML₁ receptors: Mel_{1a}, Mel_{1b} and Mel_{1c} [11]. Mel_{1a} and Mel_{1b} are now referred to as MT₁ and MT₂ receptors. These are G protein coupled receptors.

The ML₂ (also called MT₃) receptor has been identified as a form of quinine reductase [12]. Melatonin also appears to be the natural ligand for the orphan nuclear receptor superfamily RZR/ROR. The nuclear receptors may be related to melatonin's immunomodulator functions [13].

Physiological functions of melatonin:

Every night, human and other mammals secrete melatonin, a hormone which conveys a message of darkness to each and every body cell. Melatonin promotes sleep by inhibiting the drive for wakefulness which originates from the SCN [14]. Melatonin acts to quiet the SCN at night, providing a level of security and prevents stray bursts of neural activity from resetting the clock.

The hormone regulates reproduction, circadian rhythms, immunoresponsiveness and inhibits aging and cancer growth [15]. Melatonin modulates the immune system via membrane and nuclear receptors. T and B lymphocytes, natural killer (NK) cells and monocytes are activated. There is release of cytokines (IL-1, IL-2, IL-6, IL-12 and IFN γ), met-enkephalin and antiapoptotic effects. In the small intestine, a physiological role can be the modulation of intestinal motility and coordination and regulation of the process of digestion and absorption [16].

Melatonin exerts significant antioxidative protection. Numerous studies have shown the protective effect in both cell culture and 'in vivo' systems [5,17]. Neuroprotection is a special and important aspect of antioxidant protection. The antioxidant enzymes like glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase are up regulated while the prooxidant enzymes like nitric oxide synthase and lipoxygenase are down regulated [5].

In the mitochondria, melatonin safeguards the respiratory electron flux, reduces oxidant formation and inhibits opening of the mitochondrial permeability transition pore (mtPTP).

Involvement in disease states:

Melatonin secretion undergoes a predictable change with advancing age. Maternal melatonin crosses the placenta and reaches the fetus. After birth melatonin is not secreted till the baby is three months of age. Melatonin levels are highest in young children and start declining around puberty [2]. The mean circulating level in the elderly are significantly lower than that in young, healthy adults [18]. Changes in melatonin levels as

a result of aging, medications or pathological conditions may play an important role in sleep pathology.

Studies have shown a decline in melatonin concentration in the cerebrospinal fluid of patients suffering from Alzheimer's disease [19]. Studies in ischemic stroke patients have shown a disruption of the nocturnal rhythm of melatonin secretion and impaired cell-mediated immunity [20]. Decreased melatonin levels have also been reported in epileptics [9].

Melatonin levels were decreased in preganglionic sympathetic dysfunction (Shy-Drager syndrome), idiopathic orthostatic hypotension and the nocturnal rise of plasma melatonin is decreased or absent [21]. Changes have also been reported in diabetics suffering from autonomic neuropathy [22]. Melatonin may be implicated in the pathogenesis of migraine, menstrual migraine, cyclic and chronic migraine [23].

In seasonal affective disorder (SAD) there is a delay of around 2 hours in the early morning decrease of plasma melatonin [24]. Studies have found a consistent reduced daily secretion of melatonin in depressed patients [25]. Decreased serotonergic and norephinergeric stimulation of the pineal gland has been identified and a limited availability of L-tryptophan, a melatonin precursor has been postulated [26]. A study by Sandyk and coworkers had suggested that a subnormal level of melatonin may be a marker of a subgroup of schizophrenia which is characterized by negative symptoms, impaired cognitive development and poor response to neuroleptics [27]. In bipolar mood disorders, the depressive phase shows reduced melatonin secretion while the opposite is seen in the manic phase [26]. Preliminary studies had shown decreased nocturnal levels of plasma melatonin in coronary heart disease [28] and acute myocardial infarction [29]. Melatonin may be involved in the circadian rhythm of blood pressure.

Melatonin has been shown to inhibit tumorigenesis in a variety of experimental models of neoplasia [30]. Melatonin's anticancer effects may be because of inhibition of cell proliferation and stimulation of apoptosis and differentiation. In modern societies it has been postulated that artificial lighting at night suppresses melatonin secretion and increases the risk of development of cancers.

Clinical uses:

Jet lag: Randomized, placebo controlled human trials suggest that oral melatonin, started on the day of travel close to the target bedtime of the destination and continued for several days reduces the time required to establish a normal sleep rhythm, reduces sleep latency and day time fatigue and improves alertness [31]. Entrainment to the new sleep/wake cycle of the destination requires the phase-shifting of circadian rhythms. Appropriately timed superimposed light and melatonin can be used as zeitgebers to promote adaptation [32].

Delayed sleep phase syndrome (DSPS): DSPS results in delayed sleep onset despite the sleep architecture and duration being normal. Small controlled studies and case series

using a melatonin dose of 5 mg have reported improvements in sleep latency [33,34]. The use is based on the ability of exogenous melatonin to phase advance circadian rhythms.

Insomnia in the elderly: Melatonin taken orally 30 to 120 minutes before bedtime decreases sleep latency in elderly insomniacs [35,36]. Low doses (0.1 to 0.3 mg) appear to be as effective as high doses (3 to 5 mg). Melatonin has a low toxicity and does not cause locomotor or memory impairment or grogginess in the morning [2]. Melatonin gradually increases sleepiness and maintains it for a long period of time and does not substantially change the sleep architecture and has distinctively subtle effects on sleep.

Tapering of hypnotics: Melatonin has been used to assist the tapering of benzodiazepines (diazepam, lorazepam) after chronic use and initial results are promising [37]. However, further studies are required.

Cancer treatment: Several controlled trials have been carried out in patients with advanced cancers of the brain, breast, colorectal, gastric, liver, lung as well as with lymphoma, melanoma and soft-tissue sarcomas [38]. Melatonin has been combined with different treatment modalities and has been administered orally, intravenously or intramuscularly. The anticancer effect as detailed previously has been postulated to be due to antioxidant, immunostimulating, hormonal, anti-inflammatory, anti-angiogenic, apoptotic, or direct cytotoxic actions of melatonin. There has been an isolated report of tumor growth stimulation especially on administering melatonin in the morning [39].

Amelioration of the toxicity of cancer chemotherapy: Human trials have examined the effects of melatonin on the side effects of various anticancer drugs (like cisplatin, daunorubicin, doxorubicin and etoposide) [38]. Reduction in neuropathy, stomatitis, cachexia and thrombocytopenia has been reported. However, the status is controversial and some authors are of the opinion that melatonin decreases the effectiveness of chemotherapy.

Entraining circadian rhythms in the blind: The retino-hypothalamic tract plays an important role in entraining the secretion of melatonin to the light-dark cycle. In blind individuals there may be free running circadian rhythms and a non-24 h sleep-wake disorder. Multiple small case series and case reports suggest that melatonin administered in the evening may entrain circadian rhythms [40,41]. It should be reinforced by regular bedtime and structured day time activities.

Sleep disturbances associated with depression: Limited research has shown that melatonin improves the sleep patterns in patients with depression [42]. However, further studies are required.

Hypertension: Controlled studies in patients with hypertension report small reductions in diastolic and systolic blood pressure while taking melatonin orally or intranasally [43]. Repeated but not single bedtime melatonin administration significantly reduced sleep blood pressure in male patients with untreated uncomplicated essential hypertension [44]. Future studies in larger patient groups should be performed to define characteristics of

patients who would benefit most from melatonin intake. Support of circadian pacemaker function involved in blood pressure regulation may provide a new treatment strategy.

Preoperative sedation or anxiolysis: Controlled studies have compared melatonin with placebo and benzodiazepines for sedation and anxiolysis before administering general anesthesia prior to surgery [45]. Melatonin was shown to be as effective as benzodiazepines. Further studies are required.

Seizure disorder in children: The role of melatonin in seizures is controversial. Children with intractable seizures have improved with the nighttime administration of melatonin [46,47]. However, there has been a report that melatonin may lower seizure threshold and increase seizure risk [48]. Further studies are required.

Neurodegenerative disorders: Oxidative stress and free radical generation resulting from impairment of mitochondrial function and metabolism of levo-dopa and dopamine may play a role in the etiology and progression of Parkinson's disease (PD). Melatonin has potent antioxidant action and has been shown to be effective in both in vivo and in vitro models of PD [49].

However, some studies had shown that melatonin may not be effective and may worsen the condition [50]. Decreasing the bioavailability of melatonin using a receptor antagonist has been found to restore behavioral and regulatory function in PD [50]. Further research is required.

A deficiency of melatonin in the cerebrospinal fluid may be an etiologic factor for Alzheimer's disease (AD). Initial trials have shown that administration of melatonin significantly slows the progression of AD [51]. Cardinali and coworkers showed that a daily dose of 3 mg melatonin was useful in patients with Alzheimer type dementia [52]. Melatonin inhibits amyloid deposition.

Stroke: The brain is deficient in oxidative defense mechanisms and is at a greater risk of damage by reactive oxygen species (ROS). Oxidative stress has been implicated in the development of neurodegenerative disorders and brain damage caused by stroke. Melatonin may protect the brain against oxidative stress [53].

In animal models of ischemia/reperfusion injury in the brain, endogenously produced and externally administered melatonin has been shown to reduce the degree of tissue damage and limit neurological deficits [54]. At the present time, the effects of melatonin supplementation immediately after stroke are unclear in humans.

Radioprotective agent: The hydroxyl radical scavenging ability of melatonin was the rationale for testing it as a radioprotective agent. Melatonin has been shown to protect against the harmful effects of radiation in both in vitro and in vivo studies [55]. A randomized phase II clinical trial of Radiation Therapy Oncology group is ongoing in class II patients with brain metastasis. The trial compares whole-brain radiotherapy and

morning vs. evening administration of melatonin (20 mg). Melatonin has been hypothesized to be effective in protecting populations against radiation terrorism.

Work shift sleep disorder: Melatonin was not significantly better than placebo in physicians working night shifts. Seven individuals slept better with melatonin and 6 with placebo. For night-time alertness, the subjects reporting a difference were more alert with melatonin compared to placebo [56]. A similar result was reported among 22 paramedics working night shifts [57]. Additional research is necessary for drawing definite conclusions.

The dosage schedule of some of the indications of melatonin are listed in Table 1.

Table 1. Indications and dosage

Indications	Indications	Dosage
Melatonin	Solid tumors (predominantly non-small cell lung cancer and colorectal carcinoma) ⁵⁸	20 IM daily (3 pm) for 2 months (induction phase), followed by oral doses of 10 milligrams daily until progression
	For alleviation of jet lag in normal passengers (eastward or westward flights) ⁵⁹	5 mg daily for 3 days prior to departure (between 10 am and 6 pm local time), then 5 milligrams for 4 additional days (usually between 10 pm and midnight local time), beginning on the day of the flight
	Metastatic renal cell carcinoma ⁶⁰	combination of human lymphoblastoid interferon 3 million units IM 3 times weekly plus oral melatonin 10 mg once daily (6 pm), continued until tumor progression
	Sleep disorders in blind patients ⁶¹	5 mg orally at the usual bedtime has been useful in treating blind patients with desynchronized sleep-wake cycles
	Chronic insomnia ⁶²	7.5 mg oral
	Delayed phase sleep syndrome ⁶³	5 mg oral daily at 10 pm (5 hours before mean time of sleep onset prior to therapy)
Ramelteon	Insomnia* ⁶⁴	8 mg oral taken within 30 min of bedtime

*= Approved by the US FDA

Pharmacokinetics of melatonin:

Various doses have been used in different studies and for different indications. The dose has varied from 0.1 to 50 mg. There are considerable interindividual variations in plasma melatonin levels and the toxicity of melatonin is minimal [64]. The oral bioavailability of melatonin varies from 3% to 76% and the drug undergoes significant first-pass metabolism.

Adverse reactions:

Tachycardia and tachyarrhythmias have been reported. Occasional vasodilatation and pruritis may occur. Large doses of melatonin (30 mg) can cause hyperprolactinemia and may be associated with both female and male infertility. There have been reports of gynecomastia, increased insulin resistance and decreased luteinizing hormone levels. Hypothermia, confusion, dysphoria, sedation, drowsiness and fatigue may occur. Discontinuation of a 5 mg dose resulted in emergent dyskinesia and akathisia in a 22 year old woman suffering from spastic diplegia and severe mental retardation [65].

Drug-drug interactions:

Fluvoxamine may inhibit melatonin elimination or metabolism via cytochrome P450 1A2 or 2C19. Patients taking fluvoxamine and melatonin together should be monitored closely for sleep changes and central nervous system depression.

Hypertensive patients well controlled on nifedipine experienced a rise in blood pressure when melatonin was given concurrently. Melatonin may compete with nifedipine for calcium channels. On coadministration with warfarin there is an increased risk of bleeding. Concomitant use of the two drugs should be avoided and if both are taken together then the prothrombin time and international normalized ratio (INR) should be monitored and signs and symptoms of excessive bleeding should be looked for. Some of the common drug interactions of melatonin and ramelteon are listed in Table 2.

Agonists and antagonists at the melatonin receptor:

Melatonin has a short half-life and is extensively metabolised. Melatonin, a natural product cannot also be patented. Several groups have developed analogs that act as agonists or antagonists at the melatonin receptors. Agonists have shown the greater therapeutic potential and three agonists are furthest along in clinical development.

Agomelatine (S20098):

Considering the problems with the classical antidepressants, better tolerated, more effective and more rapidly acting drugs are required. Agomelatine has proven to be an efficacious antidepressant [66]. The drug is a high-affinity agonist at the MT₁ and MT₂ receptors [67]. Agomelatine is also an antagonist at the 5-HT_{2C} and 5-HT_{2B} receptors [68]. The drug has also shown promise for the treatment of anxiety disorders [69]. The drug is able to facilitate re-entrainment of circadian rhythms in response to a phase shift of the light-dark cycle.

Table 2. Drug interactions

	Interacting drugs	Outcomes	Probable mechanism	Monitoring parameters
Melatonin	Fluvoxamine	Increased CNS depression	Inhibition of cytochrome P450 enzymes, possibly CYP1A2 and CYP2C19, responsible for melatonin metabolism	Monitor for changes in sleep patterns and signs of excessive CNS depression.
	Nifedipine	Increased blood pressure	Competition of melatonin with nifedipine for calcium channels	Close monitoring of blood pressure is advised with appropriate dose adjustment of nifedipine or withdrawal of melatonin.
	Warfarin	Increased risk of bleeding	Unknown	Avoid concomitant use of melatonin and warfarin. If both are taken together, monitor prothrombin time, INR, and signs and symptoms of excessive bleeding frequently.
Ramelepton	Fluconazole	Increased risk of side effects due to ramelteon	Fluconazole inhibition of CYP2C9 and CYP3A4-mediated ramelteon metabolism	Monitor for signs and symptoms of ramelteon toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia
	Fluvoxamine	Increased risk of side effects of ramelteon	Fluvoxamine inhibition of CYP1A2-mediated ramelteon metabolism	Monitor for signs and symptoms of ramelteon toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia
	Ketoconazole	Increased risk of side effects of ramelteon	Ketoconazole inhibition of CYP3A4-mediated ramelteon metabolism	Monitor for signs and symptoms of ramelteon toxicity including somnolence, dizziness, fatigue, nausea, headache and insomnia
	Rifampin	Decreased bioavailability of ramelteon	Rifampin induced cytochrome P450 metabolism of ramelteon	Monitor patients for lack of ramelteon efficacy

Ramelteon (TAK 375):

Ramelteon has high selectivity and affinity for MT₁ and MT₂ receptors [70]. It has a longer half life than melatonin. The sleep-promoting effects are due to activity at MT₁ and MT₂ receptors. The drug was developed for the treatment of sleep-onset insomnia [71]. Ramelteon does not appear to cause rebound insomnia or withdrawal symptoms after prolonged use and can be prescribed for long-term treatment. Drug interactions have been noted with fluvoxamine, fluconazole, ketoconazole and rifampin.

Well-controlled studies in pregnant women are lacking and animal studies had shown adverse effects on the fetus. The manufacturer recommends that ramelteon be avoided by lactating mothers.

LY 156735:

This compound is a β -substituted melatonin analog and reduced sleep-onset time in patients with moderate sleep-onset insomnia [72]. The drug is in early development.

MT₁ selective agonists 35 and 134, MT₁ selective antagonists 117 and 131 and the MT₂ selective agonists 58, 70, 79, 97 and 125 and the MT₂ selective antagonists 27, 73 and 119 are undergoing characterization and animal testing [73]. New blockers like BMS-214778 and luzindole are in development and may be useful in various disorders [74,75].

Melatonin could play the role of a universal endogenous synchronizer. The influence of melatonin on hemostasis, glucose homeostasis, phosphate and calcium metabolism and regulation of blood pressure should be investigated further. The genetic control of melatonin secretion and possible side effects of chronic use should be evaluated. Melatonin and melatonin receptor agonists and antagonists will play an important role in future therapeutics.

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